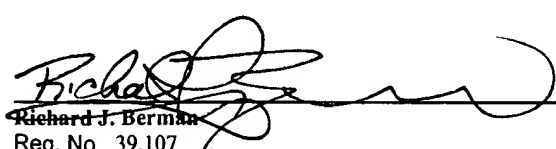


FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. P108172-00022
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		DATE: December 4, 2000
		U.S. APPL. NO. 09/701395 (IF KNOWN, SEE 37 C.F.R. 1.51) Not yet assigned
INTERNATIONAL APPLICATION NO. PCT/US99/12121	INTERNATIONAL FILING DATE June 2, 1999	PRIORITY DATE CLAIMED June 2, 1998
TITLE OF INVENTION: GENES OF CAROTENOID BIOSYNTHESIS AND METABOLISM AND METHODS OF USE THEREOF		
APPLICANT(S) FOR DO/EO/US: Francis CUNNINGHAM and Zairen SUN		
<ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. (THE BASIC FILING FEE IS ATTACHED) 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). 4. <input checked="" type="checkbox"/> A proper demand for International Preliminary Amendment was made by the 19th month from the earliest claimed priority date. 5. <input checked="" type="checkbox"/> A copy of the International Application as filed [35 U.S.C. 371(c)(2)] <ol style="list-style-type: none"> a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). <input type="checkbox"/> A translation of the International Application into English [35 U.S.C. 371(c)(2)]. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)] <ol style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input checked="" type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]. <input type="checkbox"/> An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)]. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)]. <p>Items 11 - 16 below concern other document(s) or information included:</p> <ol style="list-style-type: none"> 11. An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included. 13. <input type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input checked="" type="checkbox"/> Other items or information: Copies of International Prel. Examination Reports (2); PCT/IB/308; PCT/IPEA/408; PCT/IB/332; Copy of Response to Written Opinion dated June 14, 2000; Statement; Computer readable form and paper copy of sequence listing; copy of published application (WO 99/63055) CHINA Drawings (45 sheets) 		

525 Rec'd PCT/PTO 04 DEC 2000

U.S. APPLICATION (IF KNOWN) SEE 37 C.F.R. 1.50) Not yet assigned		INTERNATIONAL APPLICATION NO. PCT/US99/12121		ATTORNEY DOCKET NO. 108172-00022	
				DATE: December 4, 2000	
17. <input checked="" type="checkbox"/> The following fees are submitted: Basic National Fee [37 C.F.R. 1.492(a)(1)-(5)]: Search Report has been prepared by the EPO or JPO.....\$860.00 International preliminary examination fee paid to USPTO (37 C.F.R. 1.482).....\$690.00 No international preliminary examination fee paid to USPTO (37 C.F.R. 1.482) but international search fee paid to USPTO [37 C.F.R. 1.445(a)(2)].....\$710.00 Neither international preliminary examination fee (37 C.F.R. 1.482) or international search fee [37 C.F.R. 1.445(a)(2)] paid to USPTO.....\$1,000.00 International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....\$ 100.00				CALCULATIONS PTO USE ONLY <hr/>	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$ 690.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date [37 C.F.R. 1.492(e)].				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	8 - 20 =	00	X \$ 18.00	\$	
Independent Claims	2 - 3 =	00	X \$ 80.00	\$	
Multiple dependent claim(s) (if applicable)			+ \$270.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$ 690.00	
Reduction by one-half for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. 1.9, 1.27, 1.28).				\$	
SUBTOTAL =				\$ 690.00	
Processing fee of \$130.00 for furnishing the English translation later the <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date [37 C.F.R. 1.492(f)].				\$	
TOTAL NATIONAL FEE =				\$ 690.00	
Fee for recording the enclosed assignment [37 C.F.R. 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). \$40.00 per property				\$	
TOTAL FEES ENCLOSED =				\$ 690.00	
				Amount to be refunded	\$
				Charged	\$
a. <input type="checkbox"/> A check in the amount of \$ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 01-2300 in the amount of \$690.00 to cover the above fee. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2300.					
NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive [37 C.F.R. 1.137(a) or (b)] must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: Arent Fox Kintner Plotkin & Kahn 1050 Connecticut Avenue, N.W. Suite 600 Washington, D.C. 20036-5339 T l: (202) 857-6000 Fax: (202) 638-4810					
 Richard J. Berman Reg. No. 39,107					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
AS THE RECEIVING OFFICE
WITH INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

In re the application of:

UNIVERSITY OF MARYLAND, et al.

PCT International Application Number: PCT/US99/12121

Filed: June 2, 1999

For: GENES OF CAROTENOID BIOSYNTHESIS AND METABOLISM AND METHODS
OF USE THEREOF

RESPONSE TO WRITTEN OPINION

Commissioner of Patents
Box PCT
Washington, DC 20231

June 14, 2000

Sir:

This is a reply to the Written Opinion dated April 14, 2000 pursuant to PCT Rule 66.

The applicant respectfully requests that the Examiner reconsider the Written Opinion.

Novelty

Applicant respectfully disagrees that claims 1-5, 7 and 8 lack novelty as being anticipated by WO 97/36998 (hereinafter referred to as WO '998). The Written Opinion's holding of lack of novelty is based on the teaching of SEQ ID NO:1 taught by WO '998. The Written Opinion asserts that SEQ ID NO:1 of WO '998 meets the limitations of claims 1 and 2. Applicant respectfully traverses the reasoning of the Written Opinion.

Claims 1-5, 7 and 8 require

(a) a protein having lycopene epsilon-cyclase enzyme activity and an amino acid sequence which is **at least 85% identical** to the amino acid sequence of SEQ ID NO: 23, 25 or 26,

- (b) a nucleic acid encoding such a protein,
- (c) a vector comprising such a nucleic acid, or
- (d) a host cell containing such a vector.

The amino acid sequence of SEQ ID NO:1 of WO '998 does not meet the limitation of "an amino acid sequence which is at least 85% identical to one of SEQ ID NO: 23, 25 or 26" in the instant claims. A comparison of the amino acid sequence of *Arabidopsis* epsilon-cyclase, which is the protein of SEQ ID NO:1 of WO '998, and the amino acid sequence of SEQ ID NO:25 of the present application is shown in Figure 16 (see page 7, lines 26-27, of the present application). Applicants have enclosed results of GAP of

(A) *Adonis* epsilon cyclase #5, which is the amino acid sequence of SEQ ID NO:23 (see page 7, lines 19-20) of the present application and the amino acid sequence of *Arabidopsis* epsilon-cyclase, which is the protein of SEQ ID NO:1 of WO '998 (see pages i and ii attached);

(B) potato epsilon cyclase, which is the amino acid sequence of SEQ ID NO:25 (see page 7, lines 21-22) of the present application and the amino acid sequence of *Arabidopsis* epsilon-cyclase, which is the protein of SEQ ID NO:1 of WO '998 (see page iii attached); and

(C) chimeric lettuce/potato epsilon cyclase, which is the amino acid sequence of SEQ ID NO:26 (see page 7, lines 22-23) of the present application and the amino acid sequence of *Arabidopsis* epsilon-cyclase, which is the protein of SEQ ID NO:1 of WO '998 (see pages iv-v attached).

The GAP analysis shows that SEQ ID NO:1 of WO '998 has only less than 77% identity with the amino acid sequence of SEQ ID NO: 23, 25 or 26. Thus, SEQ ID NO:1 of WO '998 does not meet the amino acid sequence requirement of the instant claims. As a result, applicant submits that claims 1-5, 7 and 8 are novel.

Applicant also submits that claims 1-5, 7 and 8 have inventive step because there was no suggestion in the prior art or motivation to modify the amino acid sequence of SEQ ID NO:1 of WO '998 to make the amino acid sequence to be at least 85% identical to SEQ ID NO: 23, 25 or 26 of the present invention.

Inventive Step

The Written Opinion asserts that claim 6 lacks inventive step as being obvious over WO '998 based on the amino acid sequence of SEQ ID NO:1. Applicant respectfully traverse the holding. Applicant submits that claim 6 has inventive step because there was no suggestion in the prior art or motivation to modify the amino acid sequence of SEQ ID NO:1 of WO '998 to make the amino acid sequence to be at least 85% identical to SEQ ID NO: 23, 25 or 26 of the present invention to arrive at the invention of claim 6.

Conclusion

With the above reasoning and the attached GAP results, applicant requests that the Examiner withdraw the lack of novelty and lack of inventive step holdings.

Respectfully submitted,

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC

King L. Wong

King L. Wong
Attorney for Applicant
Registration No. 37,500

Atty. Docket No. 108172-09023

1050 Connecticut Avenue, N.W.
Suite 600
Washington, D.C. 20036-5339
(202) 857-6000

Enclosures: GAP Results (pages i-v)

Our reference: LS95033
Your reference F108172-09023

GAP of: Adonis epsilon cyclase #5 vs Arabidopsis epsilon cyclase

Gap Weight: 8 Average Match: 2.912
Length Weight: 2 Average Mismatch: -2.003
Quality: 1941 Length: 536
Ratio: 3.704 Gaps: 5
Percent Similarity: 78.764 **Percent Identity: 72.587**

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

```
1 MELLGVRNL...ISSCPVWTFGTRNLSSSKLAYNIHRYGSSCRVDFQVR 46
| . | | | : | | . : . | : | | |
1 MECVGARNFAAMAVSTFPSWSCRRKFPVVKRYSYRNIRFG.LC....SVR 45

47 ADGG..SGSRSSVAYKEGFVDEEDFIKAGGSELLFVQMQOTKSMEKQAKL 94
| | | | | | | | | | | | | | | | | | | | | | | | | |
46 ASGGGSSGSESCVAVREDFADEEDFVKAGGSEILFVQMQNQKMDDEQSKL 95

95 ADKLPPPIPFGESVMDLVVIGCGPAGLSLAAEAAKLGLKVGLIGPDLPTN 144
| | | | | | | | | | | | | | | | | | | | | | | | | |
96 VDKLPPISIGDGALDHVVIGCGPAGLALAAESAKLGLKVGLIGPDLPTN 145

145 NYGVWEDEFKDLGLERCIEHAWKDTIVYLDNDAPVLIGRAYGRVSRHLLH 194
| | | | | | | | | | | | | | | | | | | | | | | | | |
146 NYGVWEDEFNDLGLQKCIHVWRETIVYLDLDDDKPITIGRAYGRVSRLLH 195

195 EELLKRCVESGVSYLDSKVERITEAGDGHSLVVCENEIFIPCRLATVASG 244
| | | | | | | | | | | | | | | | | | | | | | | | | |
196 EELLRRCVESGVSYLSSKVDSITEASDGLRLVACDDNNVIPCRLATVASG 245

245 AASGKLLLEYEVGGPRVCVQTAYGVEVEVENNPYDPNLMVFM DYRDYMQQK 294
| | | | | | | | | | | | | | | | | | | | | | | | | |
246 AASGKLLQYEVGGPRVCVQTAYGVEVEVENSPYDPDQMVFM DYRDYTNK 295

295 LQCSEEEYPTFLYVMPMSPTRLFEEETCLASKDAMPFDLLKRLMSRLKT 344
. . | | | | | | | | | | | | | | | | | | | | | | | |
296 VRSLEAEYPTFLYAMPMTKSRLFFEETCLASKDVMPFDLLKTKMLRLDT 345

345 LGIQVTKVYEEESYIPVGGSLPNTQKNLAFGAAASMVHPATGYSVVRS 394
| | | . : | | | | | | | | | | | | | | | | | | | | |
346 LGIRILKTYEEESYIPVGGSLPNTQKNLAFGAAASMVHPATGYSVVRS 395

395 LSEAPKYASVIAKILKQDNSAYVVGSSAVNISMQAWSSLWPKERKRQR 444
| | | | | | | | | | | | | | | | | | | | | | | | | |
```

396 LSEAPKYASVIAEILREETTKQINS.....NISRQAWITLWPPERKRQR 439

445 AFFLFGLELIVQLDIEATRTFFRTFFRLPTWMWQFLGSSSLSSFDLVLF 494

440 AFFLFGALIVQFDTEGIRSFFRTFFRLPKWMWQFLGSTLTSGDLVLFA 489

495 MYMFVLAPNSMRMSLVRHLLSDPSGAVMVRAYLER* 530

490 LYMFVISPNLNRKGLINHLISDPTGATMIKTYLKV* 524

Our reference: L395033
Your reference F108172-09023

GAP of: potato epsilon cyclase vs. Arabidopsis epsilon cyclase

Gap Weight: 8
Length Weight: 2
Quality: 1499 Length: 529
Ratio: 3.966 Gaps: 1
Percent Similarity: 79.893 Percent Identity: 76.139

Match display thresholds for the alignment(s):

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: = 2

. = 1

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1  .DEFKDLGLQACIEHVWRDTIVYLDLDDDPILRAYGRSPHLLHELLR 49
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
151 EDEFNDLGLQKCIHVWRETIVYLDLDDDKPITIGRAYGRVSRLLHEELLR 200
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
50  RCVEAGVLYLNSKVDRIVEATNGHSLVECEGDVVIPCRFVTVASGAASGK 99
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
201 RCVESGVSYLSSKVDSITEASDGLRLVACDDNNVIPCRLATVASGAASGK 250
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
100 FLQYELGGPRVSVQTA YGVEVEVDNPNFDP SLMVFMDYRDYVRHDAQSLE 149
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
251 LLQYEVGGPRVCVQTA YGVEVEVENS PYDPDQMFMDYRDYTNEKVR SLE 300
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
150 AKYPTFLYAMPSPTRVFF EETCLASKDAMPFDLLKKKLMRLNTLGVRI 199
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
301 AEYPTFLYAMPMTKSRLFF EETCLASKDVMPFDLLKTKLMRLDLTLGIRI 350
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
200 KEIYEEESYIPVGGSLPNTEQKTLAFGAAASMVHPATGYSVVRSLSEAP 249
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
351 LKTYEEESYIPVGGSLPNTEQKNLAFGAAASMVHPATGYSVVRSLSEAP 400
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
250 KCAFLANILRQNH SKNMLTSSSTPSISTQAWNTLWPQERKRQRSFFLFG 299
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
401 KYASVIAEILREETTKQI.....NSNISRQAWDTLWPPERKRQRAFFLFG 445
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
300 LALILQLDIEGIRSF FRAFFRVPKMMWQGLGSSLSXADLMLFAFYMFII 349
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
446 LALIVQFDTEGIRSF FRTFFRLPKMMWQGLGSTLTSGDLVLFALYMFVI 495
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
350 APNDMRRGLIRHLLSDPTGATLIRTYLTF* 378
   ||||| ||||| ||||| ||||| ||||| ||||| ||||| |||||
496 SPNNLRKGLINHLISDPTGATMIKTYLKV* 524
```

Our reference: LS95033
Your reference F108172-09023

**GAP of: lettuce/potato epsilon cyclase chimera vs.
Arabidopsis epsilon cyclase**

Gap Weight: 8
Length Weight: 2
Quality: 1886
Ratio: 3.599
Length: 537
Gaps: 8

Percent Similarity: 77.395 **Percent Identity: 71.839**

Match display thresholds for the alignment(s):

| = IDENTITY
: = 2
. = 1

```
1  MECFGARNMTATMAVFTCPFRFTDCNIRHKFSLKQRRFTNLS.ASSSLRQ 49
   ||| ||| | ||| | | | | | | | | | | | | | | | | | |
1  MECVGARNF.AAMAVSTFPSWS.C..RRKFPVVKRYSYRNIRFGLCSVRA 46

50 I.KCSAKSDRCVVDKQGISVADEEDYVKAGGSELFFVQMORTKSMESQSK 98
   |. |: || :: |||||:|||||: |||||. | |: |||
47 SGGGSSGSESCVAVRE..DFADEEDFVKAGGSEILFVQMQQNKDMDEQSK 94

99 LSEKLAQIPIGNCILDVVIGCGPAGLALAAESAKLGLNVGLIGPDL PFT 148
   | :|| | |. | | ||||| ||||| ||||| ||||| |||||
95 LVDKLPPISIGDGALDHVVIGCGPAGLALAAESAKLGLKVGLIGPDL PFT 144

149 NNYGVWQDEFI GLGLEGCIEHSWKDTLVYLD DDDADPIRIGRAYGRVHRDL 198
   |||||: ||| |||: |||| |: |: ||||| || ||||| |||
145 NNYGVWEDEFNDLGLQKCIHVWRETIVYLD DDD.KPITIGRAYGRVSRRL 193

199 LHEELLRRCVESGVSYLSSKVERITEAPNGYSLIECEGNITIPCRLATVA 248
   ||||| |||||: |||| | | | | | | | | | | | | | | |
194 LHEELLRRCVESGVSYLSSKVDSITEASDGLRLVACDDNNVIPCRLATVA 243

249 SGAASGKFLEYELGGPRVSVQTAYGVEVEVDNNPFDPSLMVMFMDYRDYVR 298
   ||||| | |: ||. |||| | ||||| |||||: |. |: || | |||||
244 SGAASGKLLQYEVGGPRVCVQTAYGVEVEVENS PYDPQMVFM DYRDYTN 293

299 HDAQSLEAKYPTFLYAMPMSPTRVFF EETCLASKDAMPFDLLKKK LMLRL 348
   . ||||. ||||| ||||| . |. ||||| ||||| ||||| |||||
294 EKVRSLAEYPTFLYAMPMTKSRLFF EETCLASKDVMPFDLLKTK LMLRL 343

349 NTLGVRIKEIYEE EWSYIPVGGSLPNT EQKTLAFGAVAS MVHPATGYSVV 398
   . |||: || |. ||||| ||||| ||||| ||||| ||||| |||||
344 DTLGIRILKTYEE EWSYIPVGGSLPNT EQKNLAFGAAAS MVHPATGYSVV 393

399 RSLSEAPKCAFVLANILRQNH SKNMLTSSSTPSISTQAWN TLWPQERKRQ 448
   ||||| || | |: |||: . | . . || |||. |||| | ||||
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394 RSLSEAPKYASVIAEILREETTKQI.....NSNISRQAWDTLWPPERKRQ 438

449 RSFFLFGLALILQLDIEGIRSFFRAFFRVPKWMWQGFLGSSLSSADLMLF 498

|.|||||||. | ||||| | ||.|||||||. | |||

439 RAFFLFGLALIVQFDTEGIRSFFRTFFRLPKWMWQGFLGSTLTSGDLVLF 488

499 AFYMFIIAPNDMRRGLIRHLLSDPTGATLIRTYLTF* 535

| |||:|. |:|:| | |:|||||:|:|

489 ALYMFVISPNNLRKGLINHLISDPTGATMIKTYLKV* 524